Original Article

Sympathetic Hypertensive Syndrome: A Possible Surgically Curable Type of Hypertension

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Poorly controlled hypertension was incidentally cured after performing an endoscopic sympathetic block (ESB) in a patient with hyperhidrosis craniofacialis (HHC). A survey of the literature indicated that 30% to 40% of essential hypertension is of sympathetic origin. Patients with facial sweating associated with hypertension were then studied to determine whether blood pressure is lowered after performing ESB. Between November 2002 and July 2003, 17 hypertensive patients (13 males and 4 females) ranging in age from 22 to 62 years underwent ESB solely for HHC at the Department of Surgery of Kaohsiung Medical University, Taiwan. Their preoperative systolic blood pressure (SBP) values ranged from 170±6 to 200.7±7.6 mmHg, and their diastolic blood pressure (DBP) values ranged from 94.7±6.1 to 120.3±5.7 mmHg. Their heart rates were between 92.67±2.28 and 119.67±5.13 beats per minute (bpm). They were refractory to aggressive medical treatment, including lifestyle modifications and antihypertensive medications. Their postoperative blood pressure, heart rate and surgical outcomes were recorded. After performing ESB, HHC was cured in all 17 patients. Based on the reductions in blood pressure and heart rate, the patients could be divided into two groups, one showing high-level reductions (Group T) and one showing low-level reductions (Group S). The blood pressure of Group T (ten patients) was reduced to the range of 120.2±6.9 to 131.6±3.5 mmHg SBP and 74.8±3.1 to 85.4±4.5 DBP, and the heart rate of this group was reduced to the range of 65.36±4.63 to 85±3.60 bpm, while the blood pressure and heart rate of Group S (seven other patients) were reduced to the ranges of 145.9±5.7 to 160.5±5.5 mmHg SBP, 90±4 to 100.7±3.2 mmHg DBP, and 80±4 to 90.83±3.53 bpm, respectively. The patients in Group S were well controlled at 119.8±5.5 to 130.6±8.0 mmHg SBP and 70.1±3.8 to 84.5±5.7 mmHg DBP with a daily low-dose of calcium channel blocker. The average follow-up periods of the two groups were 17.00±2.906 and 17.43±2.37 months, respectively. We named this surgically curable form of hypertension "Sympathetic Hypertensive Syndrome" (SHS), which we define by the presence of all three of the following: 1) stage II hypertension; 2) HHC or other sympathetic disorders; and 3) heart rate ≥100 bpm. If the patient is male the reductions of blood pressure after the surgery will be better, which might be due to the link with Y chromosome. Finally, we recommend that ESB should be performed in patients with SHS, although the female would respond less satisfactorily in terms of the blood pressure. (*Hypertens Res* 2005; 28: 409–414)

***Key Words*: hypertension, hyperhidrosis, sympathectomy**

Introduction

A 62-year-old female visited our clinic due to severe hyperhidrosis craniofacialis (HHC, facial sweating) in November 2002. She had been suffering from refractory high blood pressure around 180/110 mmHg with a heart rate of about 105 bpm despite aggressive medical treatment for over 10 years.

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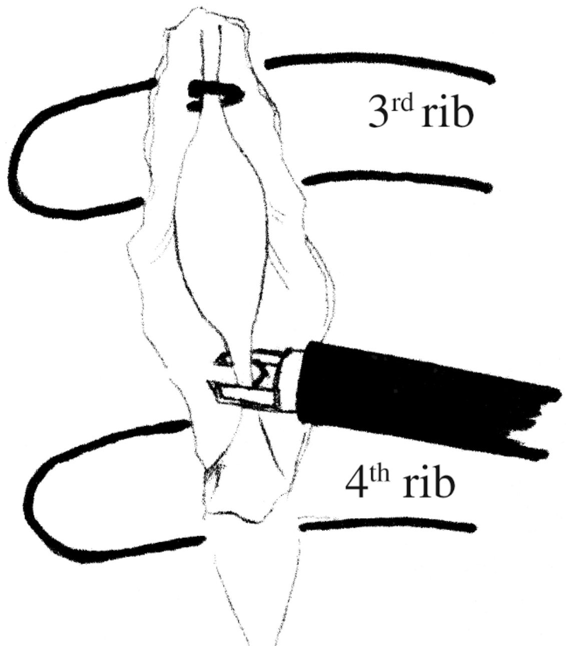

Fig. 1. *Diagram describing the clipping of T_3 sympathetic ganglion.*

We performed a bilateral T_3 endoscopic sympathetic block (ESB) for her facial sweating. After the procedure, we incidentally noticed that her blood pressure was lowered to 149.7±6.7/95.5±5.6 mmHg and was well controlled at 125.8±5.0/82±5.6 mmHg with a daily low-dose of calcium channel blocker.

The incidental amelioration of this patient's high blood pressure led us to review the subject of ESB and hypertension in the literature. Anderson *et al*. (*1*) first reported a relationship between elevated sympathetic nerve activity and hypertension in 1989. In 1995, Esler *et al*. (*2*) discussed sympathetic outflow in hypertensive humans. And in 1997, Schachter (*3*) published a review of these concepts in a monograph entitled "The Sympathetic Nervous System and Hypertension."

Based on the above, we decided to investigate the blood pressure changes after ESB for patients with HHC associated with hypertension. No similar studies have been reported before.

Methods

Between November 2002 and July 2003, 17 patients with HHC associated with hypertension who were treated at the Department of Surgery of Kaohsiung Medical University, Taiwan were enrolled in this study. Three of them also exhibited facial blushing. They included 13 males and 4 females, with ages ranging from 22 to 62 years. They had no other systemic disease. The results of a routine blood analysis and biochemical blood testing were normal. Their systolic blood pressure (SBP) values ranged from 170±6 to 200.7±7.6 mmHg, and their diastolic blood pressure (DBP) values ranged from 94.7±6.1 to 120.3±5.7 mmHg, and both were poorly controlled despite lifestyle modifications (*4*) and aggressive antihypertensive therapy. The medications administered before the surgical procedure included thiazide-type diuretics in combination with one or two of the following: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, calcium channel blocker and β-blocker. Their heart rates were between 92.67±2.28 and 119.67±5.13 bpm. All patients provided informed consent before the operation. Bilateral T_3 endoscopic sympathetic block by clipping was performed mainly for their severe facial sweating (*5*). Their blood pressures were recorded on the day after the operation, weekly in the first 2 months and followed-up monthly in the outpatient clinic for 11 to 19 months.

Preoperative Blood Pressure Measurement

Preoperative blood pressure measurement was performed as described by Bickley and Szilagyi (*6*). The examination room in the clinic was comfortable and quiet. Blood pressure was measured with a mercury sphygmomanometer with patients in a seated position after an at least 30-min rest without smoking and without drinking caffeinated beverages. An average of two readings were taken for each arm and the higher one was recorded. If the two readings differed by more than 5 mmHg, an additional one was taken.

For patients taking antihypertensives, the blood pressures were taken in three positions, *i.e.*, supine, sitting and standing. Despite their use of antihypertensive medication, all of these patients were found to have abnormally high blood pressures.

All of the measurements were made on three different occasions, and the average was taken.

For prevention of "white coat hypertension," the patients were strongly advised to check their blood pressures at home as a reference.

Operation

Endoscopic Sympathetic Block (ESB)

The ESB procedure was performed as previously described (*5*). Under general anesthesia with single lumen tracheal intubation, a two-port approach was used; one port was in the axilla and the other along the mid-axillary line at the level of the nipple. Under thoracoscopy (Karl Storz, Tuttlingen, Germany), the hooked diathermy probe was passed through the upper port. The pleura was opened along the sympathetic trunk, and the T_3 ganglion was clipped with an endoclip (Ethicon Inc., Somerville, USA) at its upper and lower ends. After finishing the entire procedure, the trocar was removed at the same time as the lung was being inflated by the anesthesiologist. No suture was necessary (Fig. 1).

Table 1. The Preoperative and Postoperative Blood Pressure and Heart Rate of Group T (*n*=10)

	Sex	Age (years)	Preoperative			Postoperative		
			Systolic (mmHg)	Diastolic (mmHg)	Heart rate (bpm)	Systolic (mmHg)	Diastolic (mmHg)	Heart rate (bpm)
A	M	38	183.7±3.2	103.7±1.5	103.67±2.52	129.4±4.2	75.6±3.5	78.00±5.69
B	M	22	170.0±6.0	100.7±2.1	101.67±4.04	124.7±3.5	80.3±2.1	80.54±4.34
C	M	32	175.3±2.5	100.3±3.1	105.33±1.66	122.8±4.2	74.9±4.4	69.38±3.78
D	M	26	188.3±5.5	105.3±3.2	100.67±1.75	121.7±11.2	79.4±3.5	85.00±3.60
E	M	29	200.7±7.6	120.3±5.7	101.67±3.82	125.9±3.9	85.4±4.5	77.78±3.78
F	M	32	184.7±3.1	104.0±2.0	109.67±3.79	131.6±3.5	80.8±2.8	79.39±2.93
G	M	25	188.3±3.8	115.3±2.1	112.33±1.53	124.4±3.2	77.4±8.5	75.54±3.83
H	M	30	178.0±6.6	102.3±2.5	104.67±3.51	120.2±6.9	74.8±3.1	65.36±4.63
I	M	35	181.7±3.2	104.3±3.5	119.67±5.13	130.7±4.1	75.3±2.4	85.00±3.00
J	M	55	179.7±3.8	100.3±3.1	100.33±2.82	130.1±4.7	80.9±5.0	74.29±0.57

Postoperative Blood Pressure Measurement (Follow-Up)

For Patients of Normal Category Pressure (4) (Group T; n=10).

In patients of Group T, postoperative blood pressure measurement was performed as described above for the preoperative measurement. The pressures were taken before discharge, then once a week for the first 2 months, and once a month in the outpatient clinic for an average of 17.00±2.90 months.

For Patients with Postoperative Stage I Hypertension (4) (Group S; n=7)

The pressure was taken weekly for 2 months during which time most of the patients were stable. A low dose (2.5 mg) of amlodipine was then prescribed. Weekly measurement was performed in three positions, *i.e.*, supine, sitting and standing, until stable and then monthly check-up for 17.43±2.370 months.

The indications of antihypertensive followed the suggestions of the Sixth Report of the Joint National Committee (*4*).

Measurement of Heart Rate

The heart rate was measured before and after the blood pressure measurement, and was taken as the average of two readings. The heart rate was verified by ECG.

Statistical Analysis

Differences in preoperative blood pressures and heart rate between the two groups were analyzed by Mann-Whitney *U* test, while differences in pre- and postoperative pressure and heart rate were analyzed and compared by Wilcoxon signed-ranks test. Pressures before and after amlodipine were also analyzed by Wilcoxon signed-ranks test. To test the categorical data, we used a χ^2 test. If the number of expected count of less than 5 were larger than 25%, we used Fisher's exact test instead. Values of *p* (two-tailed) less than 0.05 were considered to indicate statistical significance.

Results

All ESB operations were performed on an outpatient basis. Facial sweating were markedly reduced, although not completely abolished. There was no morbidity or mortality in the entire series. Although severe compensatory hyperhidrosis was noted in two patients, both of these patients were able to accept this outcome.

All patients showed significant reductions in SBP, DBP, and heart rate (Wilcoxon signed ranks test, $p=0.005$). When we further analyzed the data, we noticed an immediate postoperative reduction in blood pressure to 120.2±6.9 to 131.6±3.5/74.8±3.1 to 85.4±4.5 mmHg in ten patients (Group T). Also, the heart rates of these ten patients were reduced to 65.36±4.63 to 85.00±3.60 bpm (Table 1). The data remained stable without medication over the first 2 months, and thereafter for an average of 17.0±2.91 months. For the remaining seven patients (Group S; 3 males and 4 females), the blood pressure was around 145.9±5.7 to 160.5±5.5/90.0±4.0 to 100.7±3.2 mmHg and heart rate was 80.00±4.00 to 90.83±3.53 bpm (Table 2) in the first 2 months. Thereafter, the pressure could be well controlled to within a range of 119.8±5.5 to 130.4±8.0/70.1±3.8 to 84.5±5.7 mmHg with a daily dose of 2.5 mg amlodipine (parenthesis in Table 2), and these values were significantly different from those before administration of amlodipine (Wilcoxon signed ranks test, $p=0.018$). The differences in preoperative blood pressure between the two groups were not statistically significant (Mann-Whitney *U* test; $p=0.589$ for SBP, 0.623 for DBP). Blood pressure remained within satisfactory levels after an average follow-up period of 17.4±2.37 months. The length of the follow-up period was not significantly different between the two groups (Mann-Whitney *U* test, $p=0.731$).

Table 2. The Preoperative and Postoperative Blood Pressure and Heart Rate of Group S (*n*=7)

	Sex	Age (years)	Preoperative			Postoperative		
			Systolic (mmHg)	Diastolic (mmHg)	Heart rate (bpm)	Systolic (mmHg)	Diastolic (mmHg)	Heart rate (bpm)
K	M	52	190.3±2.1	103.3±2.7	92.67±2.28	151.4±2.1	95.7±2.3	90.65±3.21
						(129.4±1.5/84.3±4.2)*		
L	F	28	181.3±1.7	102.3±3.4	94.33±1.52	148.6±3.3	90.0±1.7	90.83±3.53
						(119.8±5.5/70.1±3.8)		
M	M	46	182.7±4.2	94.7±6.1	98.33±1.52	154.2±2.5	90.0±4.0	84.68±3.82
						(126±1/75.7±3.9)		
N	F	62	180.7±3.1	110.7±3.8	104.67±2.58	149.7±6.7	95.5±5.6	89.85±3.87
						(125.8±5.0/82±5.6)		
O	F	25	182.7±2.1	102.0±4.6	102.33±3.35	160.5±5.5	100.7±3.2	90.54±1.53
						(128.3±3.6/84.5±5.7)		
P	M	24	175.3±5.3	95.3±4.2	95.00±3.60	145.9±5.7	92.9±5.0	80.00±4.00
						(120.5±3.8/70.8±3.1)		
Q	F	32	177.7±2.3	106.0±4.6	102.33±4.04	152.8±3.9	96.2±4.1	88.83±2.77
						(130.6±8.0/75.8±2.5)		

*Blood pressure (mmHg) after 2.5 mg amlodipine.

Discussion

In review of the literature concerning the relationship between the sympathetic tone with the heart and blood vessels, Flothow (*7*) in 1952 published an article on sympathectomy for heart and coronary arteries. However, the exact mechanism is still obscure. Later, the Swedish group, Drott *et al*. (8), published their experience on sympathetic procedures in the treatment of coronary artery disease. Schachter (*3*) proposed that the sympathetic nervous system is by far the most important effector pathway in blood pressure regulation. The known neural control mechanisms of blood pressure regulation include the baroreceptor reflex, in which the ventrolateral and dorsomedial medulla in the brainstem play an important role. Also, the hypothalamus and the amygdala are the higher centers of blood pressure control.

The rostral ventrolateral medulla has positive effects on the sympathetic tone (*9–11*), while the dorsomedial medulla, mainly the nucleus tractus solitarius, acts as an inhibitor to vasoconstriction. The baroreceptor reflex works in a feedback mechanism (*3*, *12*). When the blood pressure rises, the baroreceptor in the arterial wall is stimulated, and a positive signal is sent to the nucleus tractus solitarius. From there, the inhibition to the sympathetic tone is triggered, causing a decrease in the heart rate, cardiac output and vascular tone. The result is the lowering of blood pressure. These mechanisms are illustrated in Fig. 2. The reverse series of events takes place in response to a fall in blood pressure.

A complete autonomous nervous system (ANS) response is composed of positive and negative feedback reactions (*12*): 1) efferent positive sympathetic tone from the hypothalamus and 2) afferent negative feedback sympathetic tone from target organs. In our patients, functional changes of ANS were seen after sympathetic surgery. In addition to the subsidence of facial sweating, the blood pressure was simultaneously lowered. The latter effect may have been related to the β-blocker effect of sympathetic surgery (*13*). However, the true mechanisms are still obscure.

There is evidence that up to 30% to 40% of cases of primary hypertension is due to sympathetic overactivity (*3*). However, not all hypertension can be cured through sympathetic surgery. After detailed analysis of our series, we noted the following: Group T ($n=10$) responded well to sympathetic surgery. They were all male. Nine of them were aged 22 to 38 years. The remaining male was 55 years old. Their preoperative diastolic pressure was 100.3±3.1 to 120.3±5.7 mmHg with a heart rate of 100.67±1.75 to 119.67±5.13 bpm. Group S ($n=7$) responded less satisfactorily. The lowering of pressures and heart rate of Group T was more significant than that of Group S (Mann-Whitney *U* test, $p=0.021$). Group S consisted of three males and four females. They were all maintained at a satisfactory postoperative pressure (119.8±5.5/130.6±8.0 to 70.1±3.8/84.5±5.7) with 2.5 mg amlodipine daily. The difference in blood pressure between before and after the administration of amlodipine was significant (Wilcoxon signed ranks test, $p=0.018$). The preoperative blood pressures and heart rate of the 3 males were 190.3±2.1/103.3±2.7 mmHg, 92.67±2.28 bpm; 182.7±4.2/94.7±6.1 mmHg, 98.33±1.52 bpm and 175.3±5.3/95.3±4.2 mmHg, 95.00±3.60 bpm respectively. All had a heart rate less than 100 bpm. When we compared the preoperative heart rate between Groups T and S (*i.e.*, 106.00±6.34 *vs.* 98.86±4.49 bpm), we found a significant difference (Mann-Whitney *U* test, $p=0.022$). This suggested that patients with a heart rate of over 100 bpm would show a better blood-pressure response

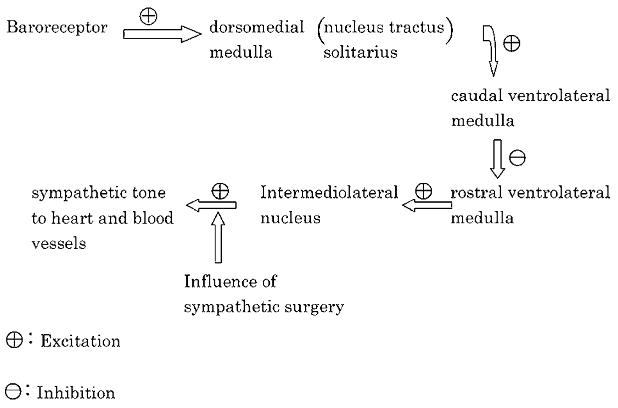

Fig. 2. *Schematic diagram showing how sympathetic surgery interrupts the pathway of sympathetic outflow.*

to sympathetic surgery. Moreover, when we compared the outcome between males and females, there was a significant difference (Fisher's exact test, $p=0.015$), with the females responding less satisfactorily.

The administration of amlodipine to Group S instead of other sympatholytic agents (*e.g.*, clonidine) was made for the following reasons. 1) Usage of amlodipine is convenient. The compliance of the people in Taiwan is not so good. Medicine administered on a once daily basis is more likely to be taken consistently. 2) As other studies (*14*, *15*), calcium channel blockers are reliable antihypertensives.

The reason that all the patients in Group T were male is still uncertain. However, one possible explanation is as follows. 1) Hypertension is considered to be a complex trait in which genetic factors play an important role (*16*, *17*). 2) Although the study of Shoji *et al.* (*18*) showed a lack of association between Y chromosome Alu insertion polymorphism and hypertension, another study (*19*) reported a link between the Y chromosome and hypertension in animals and humans. Such a link could have been responsible for the difference in responses to sympathectomy between males and females in our study. Clearly, further studies will be needed to clarify this important gender-related difference.

One interesting finding is that the improvement in blood pressure was observed almost immediately after the operation. For both groups of patients, no further change was found during the first 2 months of follow-up.

All patients benefited from sympathetic surgery in each of the following ways. First, the chief problem of facial sweating was solved. Second, blood pressure was lowered without medication or controlled with only a low-dose of amlodipine. Before the operation, most patients used two to three kinds of antihypertensives, but with poor control. Third, some associated sympathetic disorders were simultaneously solved, *e.g.*, facial blushing.

Another point that should be mentioned is that this procedure does not alter the blood pressure in normotensive patients. Although in normotensive patients, overactivity of the sympathetic nervous system also exists, *e.g.*, to the skin, their heart rates are lower than those of hypertensive patients. That is to say, the activation of the sympathetic nervous system to target organs might be different between hypertensive and normotensive patients.

A question may be raised as to why cases of palmar hyperhidrosis and axillary sweating were not included. Our answer is: Among the more than 1,000 cases that we have treated, there were no patients with hand or axillary sweating combined with hypertension.

It is expected that the present findings will provoke some controversy. However, we emphasize that the present study is purely a clinical discovery. Naturally, it would be unethical to perform a surgical control study on patients with pure primary hypertension.

Finally, we concluded that patients of hypertension respond well to sympathetic surgery if they have 1) stage II hypertension (*20*), 2) hyperhidrosis craniofacialis and (3) heart rate ≥ 100 bpm. We have given this triad the name "Sympathetic Hypertensive Syndrome." The operative results in terms of reduction in blood pressure were much better in males than females. In addition, an age of less than 40 years tended to be a positive factor, but this trend did not reach the level of statistical significance (Fisher's exact test; $p=0.25$).

Further studies with a larger number of patients and longer follow-up period will be needed to clarify the treatment mechanism of sympathetic surgery. The possibility that hypertension can be indefinitely cured by a sympathetic block would not only be a major breakthrough in medicine, but also a relief in terms of medical expenditures.

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